21. Camptothecin derivatives according to claim 1, which are 10-(4-morpholino)carbonyloxy-7-R^{1}-camptothecins.

22. Camptothecin derivatives according to claim 1, which are 11-(4-R^{4}-1-piperazino)carbonyloxy-7-R^{1}-camptothecins.

23. Camptothecin derivatives according to claim 1, which are 11-(4-C$_{1-4}$ alkyl-1-piperazino)carbonyloxy-7-R^{1}-camptothecins.

24. Camptothecin derivatives according to claim 1, which are 11-[(4-C$_{1-4}$ alkylcarbamoylmethyl)-1-piperazino]carbonyloxy-7-R^{1}-camptothecins.

25. Camptothecin derivatives according to claim 1, which are 11-[4-(1-piperidino)-1-piperidino]carbonyloxy-7-R^{1}-camptothecins.

Remarks

The Examiner has first of all required a restriction between the following groups of claims:

Group I - claims 1-17; and

Group II - claims 18-22.

The Examiner has further required that if the applicants elect the claims of Group I, then the applicants must tentatively elect a single disclosed species for initiating prosecution.

The applicants hereby affirm the previous telephone election to prosecute the claims of Group I, i.e., claims 1-17, and the election of the compound of Example 5 as the provisionally elected species for initiating prosecution. This election is, however, made without prejudice to the applicants' right to file any necessary divisional applications on the non-elected subject matter.

Claims 1, 2, 6-8, 12, 13, 15 and 16 have been rejected under 35 U.S.C. 112, second paragraph. This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

Claim 1 has been amended in order to more specifically define the compounds of the invention. Amendments have specifically been made to the definitions of R^2 and R^3 and to the recitation of the heterocyclic rings. It is believed that these actions obviate the objections raised by the Examiner in points 1, 2 and 4 on pages 3-4 of the Office Action.

The Examiner has also objected to the term "substituted" in the claims as being "non-limiting as to the number of substituents intended". Applicants, however, submit that this term is fully proper under Section 112, second paragraph. The meaning of the word "substituted" is clearly understandable to

those skilled in the art reading the claims in the application and does, accordingly, "particularly point out and distinctly claim the subject matter which the applicants regard as their invention". The meaning of the term "substituted" as used in the claims is additionally fully explained in the specification with reference to possible substituent groups and numerous possible specific compounds. The term utilized in the claim may be somewhat broad, but breadth alone does not mean that the term is indefinite. In re Gardner et al., 166 U.S.P.Q. 138 (C.C.P.A. 1970). The claims in the application utilizing the term "substituted" employ well known language conventionally used in the art, are of the same scope as the description of the invention in the specification, and are, therefore, neither vague nor indefinite. In re Kamal et al., 158 U.S.P.Q. 320 (C.C.P.A. 1968); In re Borkowski et al., 164 U.S.P.Q. 642 (C.C.P.A. 1970).

With respect to the specific amendments made to claim 1, the definition of the heterocyclic groups is fully supported by the specification at page 15, lines 21-30 and the definition of R^2 or R^3 being "heterocyclic group", or "carbocyclic group" is fully supported by the specification at page 15, lines 9-20.

Accordingly, reconsideration and withdrawal of the rejection under Section 112, paragraph 2, are respectfully requested.

Turning now to the rejection of the claims over the prior art, claims 1-17 have been rejected under 35 U.S.C. 103 over Miyasaka et al. (European Patent Application 0074256). This rejection is respectfully traversed. Reconsideration and withdrawal thereof are requested.

First of all, the Examiner is advised that the Miyasaka et al. European patent application reference corresponds to U.S. Patent 4,473,692, a copy of which is attached hereto.

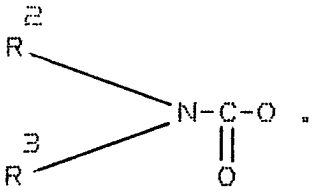
As distinguished from the Miyasaka et al. compounds, the compounds of the present invention importantly contain a substituent group in the 9-, 10- and 11-positions of ring A. In the compounds of the present invention this grouping is defined as -O-CO-X, wherein X is a chlorine atom or $-NR^2R^3$. The compounds of Miyasaka et al., on the other hand, do not contain such substituent groups. The description of Miyasaka et al. '256 at page 7 referred to by the Examiner in the Office Action relates to the substituent group R^1 in ring C, and not to the substituent groups in ring A.

But for purposes of structurally distinguishing the compounds of the present invention, it appears that the closest

comparison is with the compounds of the present invention wherein the grouping X-C-O- is bonded to the 10-position of ring A, and the compounds of Miyasaka et al. wherein the group R^3 is also bonded to the 10-position of ring A. In particular, R^3 in the Miyasaka et al. compounds may be -XR' and may be -O-acyl. Accordingly, this substituent group of the Miyasaka et al. compounds may have the structure -O-C-C- , that is where the carbon atom is directly bonded to the grouping -O-C- . The compounds of the present invention, however, contain a grouping X-C-O- , wherein the radical X is a chlorine atom or $-N(R^2)(R^3)$ such that the relevant grouping for the compounds of the present invention may be Cl-C-O- or $N(R^2)(R^3)$-C-O .

As can be seen from the above, the compounds of Miyasaki et al. even when substituted in the 10-position do not include substituents having the structure Cl-C-O- or $N(R^2)(R^3)$-C-O as

in the present invention. The Examiner has alleged in the Office Action that the acyloxy group in the 10-position for the compounds of Miyasaka et al. are similar to the grouping X-CO-O- in the present invention when the acyl moiety is derived from alkanoic, aromatic carboxylic, heterocyclic carboxylic, alkylsulfonic and aromatic sulfonic acids as described on page 7 of the Miyasaka et al. reference. In view of the description on page 8, lines 5-7 of the Miyasaka et al. reference, the substituent group XR' in the 10-position of the Miyasaka et al. compounds may be considered to be XR^1 wherein R^1 is an acyl group and X is an oxygen atom. However, for the reasons discussed above, it is clear that this substituent group in the 10-position of the Miyasaka et al. compounds never includes the important structures for the substituents of the compounds of the present invention having the structure Cl-C(=O)-O- or



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In view of the above, it is believed that the compounds of the present invention are clearly structurally distinguishable from the compounds of Miyasaka et al.

In addition to the differences in structure, the compounds of the present invention exhibit unexpected and improved

characteristics and activity as compared to the compounds of Miyasaka et al.

First considering the improved characteristics, as described in the paragraph bridging pages 2 and 3 of the present specification, camptothecin and a majority of the derivatives thereof are only sparingly soluable in water and, therefore, create a problem in administration as medicaments. Among the various compounds disclosed by Miyasaka et al., those having the grouping -XR' in the 10-position are the closest comparable compounds with those of the present invention having a grouping X-C-O- in the 10-position. 7-ethyl-10-hydroxycampto-
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thecin is a typical compound of Miyasaka et al. which possesses high anti-tumor activity but is insoluble in water. The sodium salt obtained by opening the E-ring of the compound is soluble in water but the solution formed thereby is alkaline and limits its medicinal utility.

On the other hand, the majority of the compounds of the present invention form HCl salts, sulfates or methanesulfonates which are very easily soluble in water and show weak acidity. Thus the compounds of the present invention are easily applied for medicinal use.

The compounds of the present invention are additionally improved with respect to anti-tumor activity as compared to the compounds of Miyasaka et al. In particular, a comparative test has been conducted between the compounds of the present invention and those of Miyasaka et al. utilizing the following specific compounds:

Compound No.	Name
Present invention - 1	7-Ethyl-10-[4-(isopropylcarbamoylmethyl-1-piperazino]carbonyloxy camptothecin HCl-salt
Present invention - 2	7-Ethyl-10-(1-piperazino)carbonyloxy-camptothecin HCl-salt
Present invention - 3	7-Ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin HCl-salt
Miyasaka et al. - 4	7-Ethyl-10-hydroxycamptothecin Na-salt (control)

A comparative test utilizing the above compounds measuring anti-tumor activity gave the following results:

Compd. No.	Dose for the maximum T/C	T/C (%)	Number of mice alive for 40 days	TI
	mg/Kg			
1	200	>571	6/6	32(200/6.25)
2	400	>552	5/6	64(400/6.25)
3	200	>571	6/6	32(200/6.25)
4	150	190	0/6	50(150/3)

As is clear from the above, the compounds of the present invention (compound nos. 1-3) show excellent activity as

measured by the T/C values and the number of mice alive for 40 days as compared with the compound of Miyasaka et al. (compound no. 4).

In view of the above, it is believed that the applicants have shown that the compounds of the present invention are structurally distinguishable from those of Miyasaka et al. and exhibit unexpected and improved activity as compared to the Miyasaka et al. compounds. Accordingly, reconsideration and withdrawal of the rejections and early allowance of all the claims are earnestly solicited.

Pursuant to the provisions of 37 C.F.R. 1.17 and 1.136(a), the applicants hereby petition for an extension of two (2) months to October 31, 1985 for the period in which to file a response to the outstanding Office Action. The required fee of $170.00 is attached hereto.

Please charge any fees or credit any overpayment pursuant to 37 C.F.R. 1.16 or 1.17 to Deposit Account 02-2448.

Respectfully submitted,

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